ASIDE Gastroenterology

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Review Article

The Liver-Heart Axis: A Narrative Review of Clinical Implications of the MASLD Redefinition for Internists

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ARTICLE INFO

Article history:
Received 17 Dec. 2025
Received in revised form 19 Feb. 2026
Accepted 2 Mar. 2026
Published 18 Mar. 2026

Keywords:
Metabolically-dysfunction-associated steatotic liver disease
Cardiovascular disease
Liver-heart axis
Hepatic fibrosis
Cardiometabolic risk

ABSTRACT

Introduction: Metabolically-dysfunction-associated steatotic liver disease (MASLD) represents a paradigm shift emphasizing the metabolic underpinnings of hepatic steatosis and its systemic consequences. MASLD carries a substantial cardiovascular burden. This review examines the clinical implications of the MASLD redefinition for internists, with particular focus on the liver-heart axis.
Methods: We conducted a narrative review synthesizing evidence through December 2024. Literature searches were performed in PubMed, EMBASE, and Cochrane Library using terms including "MASLD," "nonalcoholic fatty liver disease," "metabolic dysfunction-associated steatohepatitis," "cardiovascular disease," and "cardiometabolic risk." Priority was given to systematic reviews, meta-analyses, and large prospective cohort studies.
Results: MASLD is associated with increased risks of coronary artery disease, myocardial infarction, heart failure with preserved ejection fraction, atrial fibrillation, and cardiovascular mortality. These associations are mediated through insulin resistance, chronic inflammation, oxidative stress, atherogenic dyslipidemia, hepatokine dysregulation, gut-derived metabolites, and genetic determinants — though substantial residual confounding by shared cardiometabolic risk factors remains. Hepatic fibrosis stage emerges as a critical amplifier of cardiovascular risk. Integrated management requires systematic case-finding, fibrosis risk stratification using validated noninvasive tools, comprehensive cardiovascular assessment, intensive lifestyle intervention, and pharmacotherapy including incretin-based therapies, sodium-glucose cotransporter-2 inhibitors, and statins.
Conclusions: Internists must adopt integrated approaches addressing both hepatic and cardiovascular manifestations of MASLD. The liver-heart axis requires recognition as an interconnected system, with cardiovascular risk management prioritized alongside hepatic care. While the MASLD nomenclature is intended to improve disease recognition and patient engagement, prospective validation of these anticipated benefits remains needed.

1. Introduction

The landscape of fatty liver disease has undergone a transformative evolution with the introduction of metabolic dysfunction-associated steatotic liver disease (MASLD) as the replacement terminology for nonalcoholic fatty liver disease (NAFLD) [1]. This nomenclature change, announced in June 2023 following a rigorous multisociety Delphi consensus process involving over 200 panelists from 56 countries, reflects more than semantic refinement. It represents a fundamental reconceptualization of fatty liver disease as an intrinsically metabolic disorder with systemic manifestations that extend far beyond the hepatic parenchyma [1, 2].

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Citation: Abdou HA, Omar SA. The Liver-Heart Axis: A narrative review of Clinical Implications of the MASLD Redefinition for Internists. ASIDE GI. 2026;2(2):26-42, doi:10.71079/ASIDE.GI.031826446

The impetus for this nomenclature revision arose from multiple limitations of the NAFLD terminology. First, the term was exclusionary, defined by the absence of other liver diseases rather than by positive diagnostic criteria [2, 3]. Second, the terminology was perceived as stigmatizing, with terms such as fatty and nonalcoholic carrying negative connotations that could affect patient engagement and care-seeking behavior [3, 4]. Third, and most critically, the previous nomenclature failed to capture the metabolic dysfunction that fundamentally drives disease pathogenesis and progression [1, 5].

MASLD now affects approximately 30% of the global adult population, with prevalence rates paralleling the worldwide epidemic of obesity, type 2 diabetes mellitus, and metabolic syndrome [6, 7]. What was once considered a relatively benign hepatic condition has emerged as a dynamic, progressive disorder intimately linked to multisystem injury, with the cardiovascular system representing its most frequent and fatal extrahepatic target [8, 9]. Cardiovascular complications, including myocardial infarction, stroke, and heart failure, frequently manifest before significant hepatic events, underscoring the silent yet pervasive nature of the MASLD-cardiovascular disease (CVD) axis [8, 10].

For internists, who serve as frontline clinicians managing patients with complex cardiometabolic disorders, understanding the new

MASLD nomenclature and its implications for cardiovascular risk stratification is paramount. The liver-heart axis encompasses both a well-characterized forward pathway – wherein hepatic metabolic dysfunction promotes cardiovascular disease through shared pathophysiological mechanisms – and a clinically important but less well-studied reverse pathway – wherein primary cardiac dysfunction drives hepatic injury through hemodynamic and congestive mechanisms [11, 12]. This review addresses both directions, recognizing that internists managing patients with advanced heart failure or cardiogenic shock will frequently encounter hepatic consequences that require integrated clinical reasoning.

This comprehensive review aims to provide internists with an updated understanding of MASLD nomenclature, to explore the mechanistic underpinnings of the liver-heart axis, to examine cardiovascular outcomes associated with MASLD, to discuss diagnostic and risk-stratification approaches, and to outline integrated management strategies that address both hepatic and cardiovascular manifestations of this multisystem disease.

2. The MASLD Nomenclature: Key Changes and Definitions

2.1. The Delphi Consensus Process

The nomenclature revision process employed a modified Delphi methodology coordinated by three major liver associations: the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Latin American Association for the Study of the Liver (ALEH) [1]. The process included four rounds of online surveys and two hybrid meetings, with participation from hepatologists, gastroenterologists, endocrinologists, primary care physicians, patient advocates, regulatory representatives, and pharmaceutical industry stakeholders [1, 2].

Consensus was defined a priori as a supermajority (≥67%) vote. Survey results demonstrated that 74% of participants supported a name change, 78% endorsed an overarching term to accommodate disease evolution, and 67% favored inclusion of a metabolic descriptor in the new nomenclature [1, 3]. An independent external committee of experts made the final recommendation on the acronym and diagnostic criteria.

2.2. Core Definitions and Diagnostic Criteria

2.2.1. Steatotic Liver Disease (SLD)

The umbrella term encompassing all causes of hepatic steatosis, diagnosed histologically or by imaging modalities [1, 2].

2.2.2. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Defined as hepatic steatosis (≥ 5% hepatic fat content) in the presence of at least one of five cardiometabolic risk factors, in the absence of other causes of hepatic steatosis [1, 13]. The five cardiometabolic risk factors include:

1. Body mass index (BMI) ≥ 25 kg/m^2 (or ≥ 23 kg/m^2 in Asian populations) or waist circumference > 94 cm in males or > 80 cm in females
2. Fasting serum glucose ≥ 100 mg/dL or 2-hour post-load glucose ≥ 140 mg/dL or hemoglobin A1c ≥ 5.7% or type 2 diabetes mellitus or treatment for type 2 diabetes
3. Blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment
4. Plasma triglycerides ≥ 150 mg/dL or lipid-lowering treatment
5. Plasma high-density lipoprotein (HDL) cholesterol < 40 mg/dL for males and < 50 mg/dL for females or lipid-lowering treatment

2.2.3. Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Replaces the term nonalcoholic steatohepatitis (NASH), referring to MASLD with histological evidence of steatohepatitis characterized by steatosis, hepatocellular ballooning, and lobular inflammation [1, 14].

2.2.4. Metabolic and Alcohol-Associated Liver Disease (MetALD)

A new diagnostic category describing individuals with MASLD who consume alcohol beyond the thresholds previously used to define NAFLD (140-350 g/week for females and 210-420 g/week for males) [1, 15]. This category acknowledges the synergistic effects of metabolic dysfunction and moderate alcohol consumption on liver disease progression.

2.2.5. Cryptogenic Steatotic Liver Disease

Reserved for individuals with hepatic steatosis who do not meet criteria for MASLD and have no other identifiable cause [1, 2].

2.3. Advantages of the New Nomenclature

The transition to MASLD offers several intended clinical and research advantages. First, the affirmative, inclusion-based diagnostic criteria eliminate the need for exclusionary diagnoses, simplifying clinical practice [3, 4]. Second, the terminology emphasizes the metabolic foundations of disease pathogenesis, aligning diagnostic nomenclature with therapeutic targets [5, 16]. Third, non-stigmatizing language is intended to improve patient engagement, reduce psychological burden, and enhance healthcare-seeking behavior. However, prospective studies are needed to validate these anticipated benefits [3, 17].

Importantly, comparative analyses demonstrate that MASLD criteria capture approximately 99% of individuals previously diagnosed with NAFLD, ensuring continuity of natural history data, clinical trial applicability, and biomarker validation [18, 19]. The new nomenclature does not alter histological staging systems or modify the definition of steatohepatitis, preserving the relevance of decades of NASH-focused research [1, 14].

3. Epidemiology and Clinical Burden of MASLD

MASLD represents the most prevalent chronic liver condition worldwide, affecting an estimated 30% of the global adult population [6, 20]. Prevalence varies geographically, with the highest rates observed in South America (44.4%), the Middle East (32%), and Asia (29.6%) [20, 21]. In industrialized nations, MASLD prevalence parallels obesity rates, with approximately 25-30% of adults in North America and Europe affected [21, 22].

The condition demonstrates a particular predilection for individuals with metabolic syndrome components. Among patients with type 2 diabetes mellitus, MASLD prevalence reaches 55-70%, while obese individuals exhibit prevalence rates of 70-90% [23, 24]. Notably, 7-20% of MASLD cases occur in non-obese or lean individuals, highlighting the complex pathophysiology beyond simple weight-related mechanisms [25, 26].

Progressive fibrosis develops in approximately 20-30% of individuals with MASLD, with 10-15% advancing to cirrhosis over 10-20 years [27]. The presence of metabolic dysfunction-associated steatohepatitis (MASH) significantly accelerates fibrosis progression, with advanced fibrosis developing in 25-35% of MASH patients [28, 29].

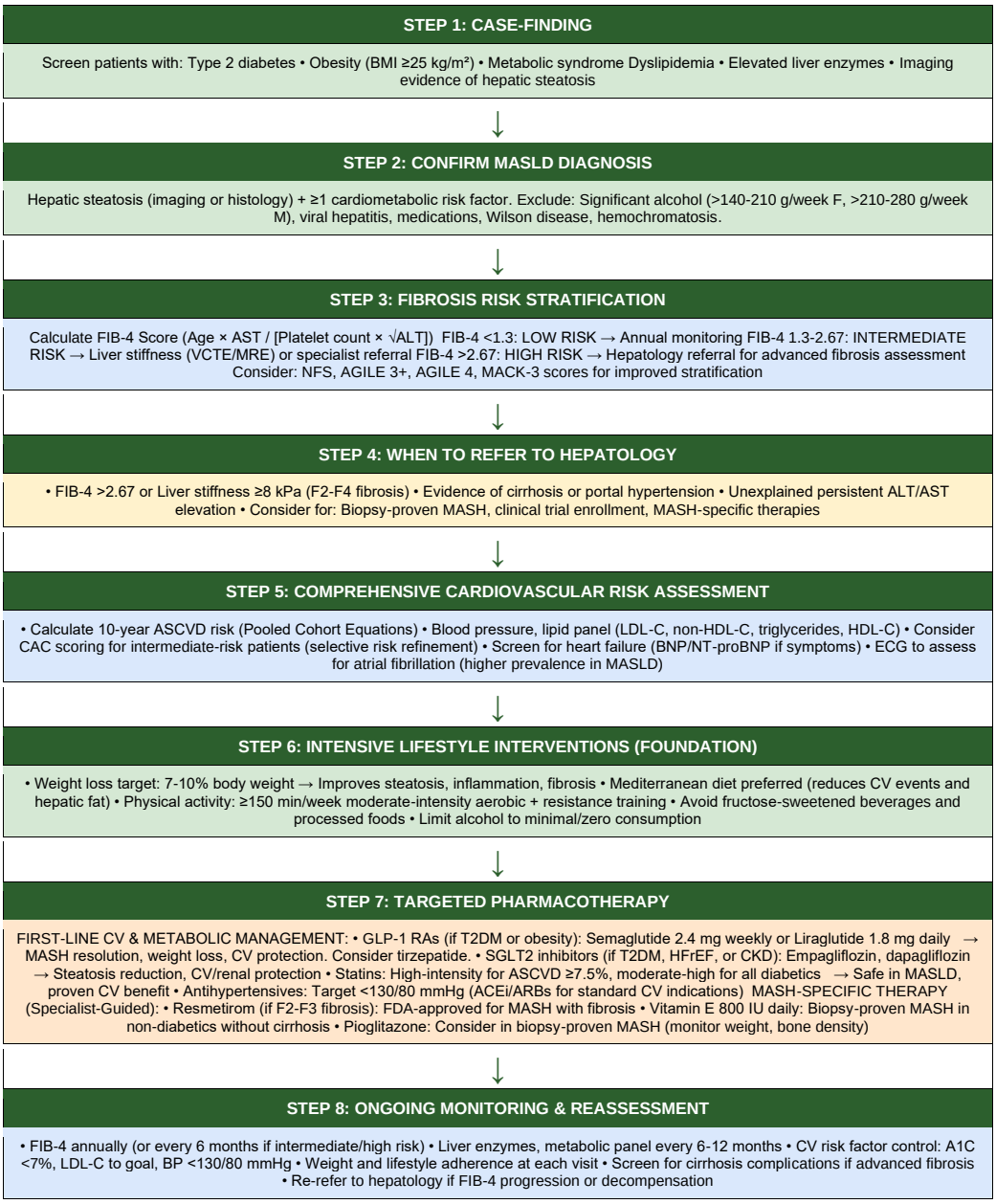

Figure 1: Integrated Management Algorithm for MASLD in Internal Medicine Practice.
Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; FIB-4, Fibrosis-4 Index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; NFS, NAFLD fibrosis score; MASH, metabolic dysfunction-associated steatohepatitis; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; BNP, B-type natriuretic peptide; ECG, electrocardiogram; T2DM, type 2 diabetes mellitus; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; A1C, hemoglobin A1C.

Critically, cardiovascular disease represents the leading cause of mortality in MASLD patients, accounting for approximately 40-50% of deaths, far exceeding liver-related mortality, which accounts for only 5-15% of deaths in non-cirrhotic MASLD [30, 31]. This epidemiological profile underscores the primacy of cardiovascular risk management in MASLD care paradigms.

4. Pathophysiological Mechanisms Linking MASLD and Cardiovascular Disease

The liver-heart axis in MASLD is characterized by complex, bidirectional interactions mediated through multiple overlapping pathophysiological mechanisms [32].

4.1. Insulin Resistance and Metabolic Dysregulation

Insulin resistance is a cornerstone pathophysiological feature linking MASLD to cardiovascular disease [33, 34]. Hepatic steatosis both

results from and perpetuates systemic insulin resistance through the release of pro-inflammatory cytokines, altered lipoprotein metabolism, and the secretion of a diverse repertoire of hepatokines – liver-derived circulating proteins that mediate inter-organ crosstalk across the liver-heart axis. These hepatokines can be broadly organized by their predominant downstream effects. Among those with primary metabolic relevance, fibroblast growth factor 21 (FGF21) is paradoxically elevated in MASLD despite its physiological role in promoting fatty acid oxidation and insulin sensitization, a state of FGF21 resistance analogous to leptin resistance in obesity. Fetuin-A and fetuin-B, both upregulated in hepatic steatosis, impair insulin receptor signaling and promote systemic insulin resistance, with fetuin-A additionally serving as an endogenous inhibitor of the insulin receptor tyrosine kinase [35]. Selenoprotein P, a hepatokine elevated in MASLD and type 2 diabetes, impairs insulin signaling in skeletal muscle and the myocardium and has been independently associated with cardiovascular risk. Sex hormone-binding globulin (SHBG), whose hepatic synthesis is suppressed by insulin resistance and hepatic fat accumulation, serves as an inverse biomarker of metabolic syndrome severity and has been associated with incident type 2 diabetes and cardiovascular disease risk. Among hepatokines with more direct vascular and lipid-trafficking relevance, angiopoietin-like proteins 3, 4, and 8 (ANGPTL3, ANGPTL4, ANGPTL8) regulate lipoprotein lipase activity and plasma triglyceride clearance; their dysregulation in MASLD contributes to atherogenic dyslipidemia and has positioned ANGPTL3 in particular as an emerging therapeutic target in cardiometabolic disease. Hepassocin, a hepatocyte-derived growth factor, promotes hepatic steatosis by upregulating lipogenic pathways and has been associated with endothelial dysfunction and early atherosclerosis. However, its precise role in the MASLD-cardiovascular axis remains to be characterized. Collectively, this hepatokine network illustrates how the steatotic liver actively remodels systemic metabolic and vascular homeostasis, extending its pathological influence well beyond the hepatic parenchyma [35, 36].

A meta-analysis involving over 500,000 participants demonstrated that insulin resistance, measured by the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), significantly elevates the risk of atherosclerotic cardiovascular disease, with each 1 standard deviation increase in HOMA-IR correlating with a 1.46-fold higher risk of developing atherosclerotic cardiovascular disease [37]. Similarly, HOMA-IR scores have been independently associated with altered left ventricular relaxation and diastolic dysfunction, affecting up to 50% of patients with type 2 diabetes [38, 39].

4.2. Chronic Low-Grade Inflammation

Hepatic steatosis triggers activation of innate immune pathways, particularly through Kupffer cells and hepatic stellate cells, resulting in production and systemic release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP) [40, 41]. These inflammatory mediators promote endothelial dysfunction, accelerate atherosclerosis, and contribute to myocardial remodeling [42, 43].

The inflammatory phase of MASLD, characterized by steatohepatitis (MASH), demonstrates particularly robust systemic inflammatory activity. Inflammatory spillover from the liver affects distant organs, including the heart, skeletal muscle, and kidneys, contributing to the multisystem impact of disease [44, 45].

4.3. Oxidative Stress and Lipotoxicity

Excess reactive oxygen species generated in lipid-laden hepatocytes and activated macrophages contribute to mitochondrial dysfunction, lipid peroxidation, and cytokine release [46, 47]. This oxidative milieu fosters the formation of oxidized low-density lipoprotein (LDL) and perpetuates vascular inflammation. Studies have linked markers of oxidative stress in MASLD with increased carotid intima-media thickness and coronary artery calcification, established precursors of clinical cardiovascular disease [48, 49].

Lipotoxicity, resulting from the accumulation of toxic lipid species including ceramides, diacylglycerols, and free fatty acids, directly impairs cardiomyocyte function and promotes cardiac fibrosis [50, 51].

4.4. Atherogenic Dyslipidemia

MASLD is characterized by a distinctive atherogenic lipid profile including elevated triglycerides, increased small dense LDL particles, reduced HDL cholesterol, and elevated apolipoprotein B [52, 53]. This dyslipidemia results from hepatic overproduction of very-low-density lipoproteins (VLDL), impaired lipoprotein clearance, and altered apolipoprotein metabolism [54, 55].

The atherogenic dyslipidemia associated with MASLD independently predicts cardiovascular events beyond traditional Framingham risk factors [56, 57].

4.5. Gut-Liver-Heart Axis

Emerging evidence highlights the roles of gut microbiome dysbiosis, increased intestinal permeability, and bacterial translocation in the pathogenesis of MASLD and cardiovascular disease [58, 59]. Patients with MASLD exhibit altered gut microbial composition, with increased abundance of pro-inflammatory taxa, including Enterobacteriaceae and Proteobacteria, and decreased abundance of beneficial commensals, including Faecalibacterium prausnitzii and Akkermansia muciniphila [60, 61].

Lipopolysaccharides (LPS) derived from gut bacteria traverse the compromised intestinal barrier, reach the liver via portal circulation, and activate toll-like receptor 4 (TLR4) signaling, triggering hepatic and systemic inflammation [62, 63]. Elevated circulating LPS levels have been associated with both MASLD severity and cardiovascular events [64, 65]. A particularly well-characterized gut-derived metabolite linking hepatic and cardiovascular pathology is trimethylamine N-oxide (TMAO). Generated when gut bacteria metabolize dietary choline, phosphatidylcholine, and L-carnitine to trimethylamine (TMA), which is subsequently oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3), circulating TMAO levels reflect the combined influence of dietary substrate availability, gut microbial composition, and hepatic oxidative capacity – all of which are altered in MASLD [59]. Elevated TMAO has been independently associated with accelerated atherosclerosis through promotion of macrophage foam cell formation and impaired reverse cholesterol transport, with enhanced platelet hyperreactivity and thrombotic risk, and with adverse cardiac remodeling and incident heart failure, including heart failure with preserved ejection fraction [64]. Patients with MASLD demonstrate elevated circulating TMAO levels compared to matched controls, and TMAO concentrations correlate with hepatic fibrosis severity, suggesting that progressive liver dysfunction amplifies TMAO generation and systemic vascular exposure [62]. While direct interventional data in MASLD remain limited, TMAO biology provides a mechanistically coherent link between gut dysbiosis, hepatic metabolic dysfunction, and the full spectrum of cardiovascular manifestations observed in this population – spanning atherosclerosis, thrombosis, and heart failure – reinforcing the clinical importance of the gut-liver-heart axis.

4.6. Hepatic Fibrosis and Cardiovascular Risk

Hepatic fibrosis stage has emerged as a critical determinant of cardiovascular risk in MASLD, often surpassing the predictive value of steatosis or steatohepatitis alone [66, 67]. Advanced fibrosis (stage F3-F4) is independently associated with increased cardiovascular events, cardiovascular mortality, and all-cause mortality [68, 69].

The mechanisms linking hepatic fibrosis to cardiovascular disease remain incompletely understood but likely involve persistent systemic inflammation, endothelial dysfunction, enhanced platelet activation, and altered hepatic synthesis of cardiovascular-protective proteins [70, 71].

4.7. Genetic Determinants and the Discordant Phenotype Problem

Common genetic variants exert substantial influence on MASLD susceptibility, fibrosis progression, and – critically – cardiovascular risk profiles, often in discordant directions, with direct clinical relevance for internists. The most studied variant, PNPLA3 I148M (rs738409), encodes a gain-of-function substitution in patatin-like phospholipase domain-containing protein 3 that impairs hepatic lipid droplet remodeling. Carriers of the G allele demonstrate accelerated hepatic steatosis, steatohepatitis, fibrosis, and hepatocellular carcinoma risk, yet paradoxically do not appear to carry a proportionally elevated cardiovascular risk, possibly because the variant promotes hepatic lipid retention rather than dyslipidemic spillover into the systemic circulation [72, 73].

The TM6SF2 E167K variant (rs58542926) illustrates this dissociation most strikingly. Loss-of-function of transmembrane 6 superfamily member 2 reduces hepatic VLDL secretion, resulting in hepatic lipid accumulation and accelerated fibrosis, while simultaneously lowering circulating triglycerides and LDL cholesterol – a profile associated with reduced atherosclerotic cardiovascular disease risk despite more severe liver disease [70, 73]. This TM6SF2 paradox exemplifies why genetic background can uncouple the liver-heart axis, and why cardiovascular risk cannot be assumed to track linearly with hepatic disease severity in all patients.

HSD17B13 loss-of-function variants confer hepatoprotection by reducing hepatic inflammatory activity and fibrosis progression, and have attracted interest as therapeutic targets, though their effect on cardiovascular risk remains under investigation [73, 74]. MBOAT7 variants similarly promote hepatic steatosis and fibrosis through altered phosphatidylinositol remodeling, with an emerging but incompletely characterized cardiometabolic profile [73].

For internists, the practical implication is that patients with discordant phenotypes – severe liver disease but favorable lipid profiles, or vice versa – may harbor underlying genetic architecture that modifies standard cardiovascular risk predictions. While routine genetic testing is not currently recommended in clinical practice, awareness of these variants helps explain phenotypic heterogeneity among patients with MASLD. It underscores the need for individualized rather than uniform cardiovascular risk assessment.

4.8. The Reverse Pathway: Cardiac Dysfunction and Congestive Hepatopathy

While the predominant focus of the liver-heart axis in MASLD literature is the forward pathway from hepatic metabolic dysfunction to cardiovascular disease, the reverse pathway – wherein primary cardiac dysfunction drives progressive hepatic injury – is of equal clinical importance for internists and represents a distinct but intersecting disease process [11, 71].

4.8.1. Hemodynamic Mechanisms

Right-sided heart failure, whether arising de novo or as a consequence of advanced left ventricular dysfunction, generates sustained elevation of central venous and hepatic venous pressures. This increased back-pressure is transmitted directly to the hepatic sinusoids via the inferior vena cava and hepatic veins, resulting in sinusoidal congestion, hepatocellular hypoxia, and zone 3 (centrilobular) necrosis – the histological hallmark of congestive hepatopathy [11, 71]. In parallel, reduced cardiac output impairs hepatic arterial perfusion, creating a dual insult of venous congestion and arterial ischemia that is particularly injurious in the setting of acute decompensation. Elevated right atrial pressure also impairs portal venous return, contributing to splanchnic congestion, gut barrier dysfunction, and bacterial translocation, which may further amplify systemic inflammation [58, 63].

4.8.2. Congestive Hepatopathy and Cardiac Cirrhosis

Chronic, sustained hepatic venous hypertension – most commonly seen in patients with heart failure with reduced ejection fraction, constrictive pericarditis, severe tricuspid regurgitation, or Fontan circulation – drives progressive hepatic fibrosis by activating hepatic stellate cells in response to persistent sinusoidal pressure and hypoxia [70, 71]. This process, termed congestive hepatopathy, exists on a spectrum from mild centrilobular fibrosis to frank cardiac cirrhosis, the latter carrying its own risks of portal hypertension, hepatic synthetic dysfunction, variceal bleeding, and hepatocellular carcinoma [71]. The fibrosis pattern of cardiac cirrhosis is characteristically reversed to that of MASLD – beginning in zone 3 (centrilobular) rather than zone 1 (periportal) – a distinction of diagnostic importance when evaluating liver biopsy specimens in patients with coexisting cardiac and metabolic disease [70].

4.8.3. Portal Hemodynamics and Clinical Consequences

As congestive hepatopathy progresses, portal hypertension may develop even in the absence of advanced parenchymal fibrosis, driven primarily by elevated hepatic venous outflow resistance rather than intrahepatic architectural distortion [71]. Clinically, this manifests as ascites, peripheral edema, and splenomegaly – findings that may be incorrectly attributed to cardiac failure alone, delaying recognition of the hepatic contribution. Hepatic synthetic function, reflected by prolonged prothrombin time, hypoalbuminemia, and hyperbilirubinemia, is impaired in advanced congestive hepatopathy and carries independent prognostic significance in heart failure patients beyond standard cardiac biomarkers [11, 71]. Serum aminotransferases are typically mildly elevated in chronic congestive hepatopathy. Still, they may rise sharply – occasionally mimicking acute hepatitis – during episodes of acute hemodynamic decompensation, a pattern sometimes termed ischemic hepatitis or shock liver [70, 71].

4.8.4. Clinical Implications for Internists

For internists, several practical points follow from recognition of the reverse pathway. First, liver function abnormalities in patients with known heart failure should not be reflexively attributed to medications or incidental hepatic disease; a hemodynamic contribution should be systematically considered, particularly when right-sided pressures are elevated [11, 71]. Second, the coexistence of MASLD and congestive hepatopathy in the same patient – increasingly common given the shared cardiometabolic substrate – creates diagnostic complexity, as fibrosis on non-invasive testing or biopsy may reflect both metabolic and congestive mechanisms [70]. Third, optimization of cardiac hemodynamics – through guideline-directed medical therapy, diuresis, device therapy, or valve intervention – represents the primary therapeutic lever for congestive hepatopathy, and hepatic parameters frequently improve with successful cardiac

management [71]. Fourth, in patients being evaluated for advanced heart failure therapies, including left ventricular assist devices or cardiac transplantation, accurate hepatic assessment is essential, as significant hepatic fibrosis or cardiac cirrhosis may influence candidacy and post-procedural outcomes [11, 71].

5. Cardiovascular Manifestations of MASLD

5.1. Coronary artery disease and Myocardial Infarction

Multiple epidemiological studies demonstrate robust associations between MASLD and coronary artery disease [75, 76]. Meta-analyses report that MASLD increases the risk of coronary artery disease by 1.5-2.0-fold after adjustment for traditional cardiovascular risk factors [32, 77]. The association strengthens with disease severity, with MASH and advanced fibrosis conferring a higher risk than simple steatosis [78, 79].

MASLD patients exhibit increased coronary artery calcification scores, higher prevalence of vulnerable plaque morphology, and greater extent of multivessel coronary disease compared to matched controls [80, 81]. Importantly, myocardial infarction risk increases progressively with the stage of hepatic fibrosis, underscoring the importance of fibrosis assessment in cardiovascular risk stratification [68, 82].

5.2. Heart Failure

MASLD demonstrates particularly strong associations with heart failure, especially heart failure with preserved ejection fraction (HFpEF) [83, 84]. Meta-analytic evidence indicates that MASLD increases heart failure risk by approximately 1.5-fold, with higher relative risks for HFpEF compared to heart failure with reduced ejection fraction (HFrEF) [85, 86].

Magnetic resonance imaging studies reveal structural and functional cardiac alterations in MASLD patients, including increased left ventricular mass, concentric remodeling, impaired diastolic relaxation, and reduced myocardial strain, even in the absence of clinically evident cardiac disease [87, 88]. Increased epicardial adipose tissue thickness, commonly observed in MASLD, promotes cardiac dysfunction through pro-inflammatory cytokine production and direct lipotoxic effects on myocardium [89, 90].

5.3. Atrial Fibrillation

Emerging evidence links MASLD to increased atrial fibrillation prevalence and incidence [91, 92]. The inflammatory milieu characteristic of MASH may foster atrial electrical remodeling, promoting arrhythmogenesis [72, 93]. Meta-analyses demonstrate that MASLD increases atrial fibrillation risk by approximately 1.4-fold, with risk amplification in patients with more severe hepatic disease [94, 95].

5.4. Stroke

Several observational studies report associations between MASLD and increased stroke risk, both ischemic and hemorrhagic subtypes [96, 97]. MASLD patients demonstrate higher carotid intima-media thickness, increased carotid plaque prevalence, and greater plaque vulnerability compared to controls. Meta-analytic estimates suggest MASLD increases stroke risk by approximately 1.3-1.5-fold [98, 99].

5.5. Cardiovascular Mortality

Critically, MASLD significantly increases cardiovascular mortality risk, which represents the leading cause of death in this population [68, 100]. Meta-analyses including over 9 million participants demonstrate that MASLD increases cardiovascular mortality risk by approximately 1.6-fold compared to individuals without MASLD [101, 102]. Risk escalates with disease severity, with MASH and advanced fibrosis conferring substantially higher cardiovascular mortality compared to simple steatosis [103, 104].

6. Diagnostic Considerations and Risk Stratification

6.1. Establishing the Diagnosis of MASLD

Diagnosis of MASLD requires documentation of hepatic steatosis through imaging or histology, plus verification of at least one cardiometabolic risk factor [1, 13]. Hepatic steatosis can be identified through multiple modalities:

6.1.1. Imaging Modalities

- Ultrasonography: Widely available, cost-effective first-line modality; sensitivity 60–94% for detecting $\geq$ 20–30% hepatic steatosis [105, 106].
- Controlled Attenuation Parameter (CAP): Adjunct to transient elastography; provides quantitative steatosis assessment [107, 108].
- Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF): Gold standard for non-invasive steatosis quantification; high accuracy for detecting $\geq$ 5% hepatic fat [109, 110].
- Computed Tomography: Can detect moderate-to-severe steatosis; radiation exposure limits routine use [111, 112].

6.1.2. Histological Assessment

Liver biopsy remains the reference standard for diagnosing MASH and staging fibrosis, although its invasive nature limits its routine use [113, 114].

6.2. Case-Finding Strategies

Current guidelines recommend case-finding for MASLD with liver fibrosis using non-invasive tests in high-risk populations, particularly individuals with type 2 diabetes, obesity with additional metabolic risk factors, abnormal liver enzymes, or radiological signs of hepatic steatosis [115, 116].

6.3. Fibrosis Assessment

Given the critical prognostic importance of hepatic fibrosis for both hepatic and cardiovascular outcomes, accurate assessment of fibrosis is essential [117, 118]. Non-invasive tools have evolved substantially, and a sequential, stepwise strategy combining simple blood-based scores with imaging-based elastography – and increasingly with newer composite scores – now allows the majority of patients to be risk-stratified without liver biopsy.

6.3.1. Non-Invasive Fibrosis Assessment

1. **Fibrosis-4 Index (FIB-4)**: Calculated using age, AST, ALT, and platelet count; cutoffs < 1.3 (or < 2.0 for age $\geq$ 65 years) reliably exclude advanced fibrosis; values > 2.67 suggest high probability of advanced fibrosis and warrant further evaluation [119, 120]. FIB-4 remains the recommended first-line triage tool in primary care and general internal medicine settings, given its simplicity, zero additional cost, and robust validation across diverse populations.
2. **NAFLD Fibrosis Score (NFS)**: Incorporates age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio; cutoff < -1.455 excludes advanced fibrosis; score > 0.676 suggests advanced fibrosis [121, 122]. NFS performs comparably to FIB-4 as a first-line triage instrument, though its BMI dependency may limit precision in patients with extreme obesity.

3. **Transient Elastography (TE)**: Measures liver stiffness as a surrogate for fibrosis; cutoff < 8 kPa excludes advanced fibrosis; values > 12–14 kPa suggest advanced fibrosis or cirrhosis [123, 124]. TE is well-validated, widely available, and reproducible, but carries important technical limitations in patients with BMI > 35 kg/m^2, narrow intercostal spaces, or significant ascites, in whom probe failure or unreliable readings are substantially more frequent. In these patients, an alternative elastography modality should be prioritized rather than accepting an indeterminate TE result.
4. **Magnetic Resonance Elastography (MRE)**: MRE measures liver stiffness through propagation of mechanical shear waves quantified by MRI, and is currently the most accurate non-invasive modality for fibrosis staging across the full spectrum from F0 to F4 [109, 110]. Critically, MRE is not subject to the BMI-related technical failures that limit TE, making it the preferred elastography modality in patients with significant obesity, prior indeterminate TE, or where precise fibrosis staging will directly influence management decisions, such as eligibility for MASH-specific pharmacotherapy or advanced heart failure evaluation. The principal limitations of MRE are cost, scanner availability, and the presence of hepatic iron, which can confound stiffness measurements [109, 110].
5. **Enhanced Liver Fibrosis (ELF) Score**: Blood-based test measuring hyaluronic acid, procollagen III N-terminal peptide, and tissue inhibitor of metalloproteinases-1; score < 9.8 excludes advanced fibrosis [125, 126]. ELF performs well as a second-line confirmatory test and is particularly useful when elastography is unavailable or technically limited.
6. **AGILE 3+ and AGILE 4**: These newer composite scores combine FIB-4 with liver stiffness measured by TE to produce a single integrated probability estimate for advanced fibrosis (AGILE 3+) or cirrhosis (AGILE 4) [127, 128]. By incorporating both biochemical and elastographic information, AGILE scores substantially reduce the proportion of patients falling into the indeterminate zone that characterizes FIB-4 or TE alone – a clinically important advance, as indeterminate results currently represent the most common reason for unnecessary hepatology referral or biopsy in primary care pathways. Validation studies demonstrate that sequential use of FIB-4 followed by AGILE 3+ can correctly rule in or rule out advanced fibrosis in a larger proportion of patients than any single test, with only a minority requiring liver biopsy for definitive staging [127, 128].
7. **MACK-3**: A composite score integrating serum markers of cell death (cytokeratin-18 fragments), fibrogenesis (PRO-C3, a marker of type III collagen synthesis), and standard biochemistry, MACK-3 is specifically designed to identify patients with active MASH and significant fibrosis – the population most likely to benefit from pharmacological intervention [126, 127]. Its utility lies particularly in distinguishing patients with simple steatosis from those with progressive steatohepatitis and fibrosis, a distinction that blood-based scores and elastography alone cannot reliably make, and it may help prioritize biopsy or treatment initiation in patients with borderline fibrosis scores.

6.3.2. Risk Stratification Pathway

Current best practice supports a sequential stratification approach. In primary care and general internal medicine, FIB-4 serves as the universal first-line triage tool. Patients with low FIB-4 values can be reassured and monitored, while those with high values should be referred to hepatology. The critical challenge lies in the indeterminate FIB-4 range (1.3 – 2.67), which encompasses a substantial proportion of patients. In this group, second-line evaluation with TE is appropriate when technically feasible; where TE is limited by obesity or yields unreliable results, MRE should be used. AGILE 3+ can be applied to integrate FIB-4 and TE results and further reduce the indeterminate fraction. MACK-3 may add value in patients in whom distinguishing active MASH from simple steatosis would alter management decisions, particularly when considering MASH-specific pharmacotherapy. Patients with evidence of advanced fibrosis on any validated pathway warrant referral to hepatology for comprehensive management and consideration of liver biopsy [129, 130].

6.4. Cardiovascular Risk Assessment

All MASLD patients require systematic cardiovascular risk evaluation incorporating [131, 132]:

1. Traditional risk factor assessment: Lipid profile, blood pressure, diabetes status, smoking history, family history of premature cardiovascular disease
2. Calculation of 10-year atherosclerotic cardiovascular disease risk using validated algorithms (e.g., Pooled Cohort Equations)
3. Evaluation for subclinical atherosclerosis through carotid ultrasound or coronary artery calcium scoring in intermediate-risk patients
4. Assessment of hepatic fibrosis stage, recognizing advanced fibrosis as a cardiovascular risk amplifier

7. Management Strategies: An Integrated Approach

7.1. Lifestyle Modification: The Cornerstone of Therapy

Lifestyle intervention targeting weight reduction, dietary modification, and increased physical activity represents the foundation of MASLD management [133, 134].

7.1.1. Weight Loss Targets

Weight reduction of 3-5% improves hepatic steatosis, while 7-10% weight loss is required to improve steatohepatitis and fibrosis [135, 136]. Greater weight loss (≥ 10%) yields more robust benefits, including regression of fibrosis [137, 138].

7.1.2. Dietary Recommendations

Mediterranean diet patterns emphasizing monounsaturated fats, omega-3 fatty acids, whole grains, fruits, vegetables, and limited processed foods improve both hepatic and cardiovascular parameters [139, 140]. Reduction of fructose-containing beverages and processed carbohydrates benefits hepatic steatosis and metabolic profiles [141, 142].

7.1.3. Physical Activity

Regular aerobic exercise (150-200 minutes of moderate-intensity activity weekly) and resistance training improve hepatic steatosis, insulin sensitivity, and cardiovascular fitness, independent of weight loss [143, 144].

7.2. Pharmacological Management of Cardiometabolic Risk Factors

7.2.1. Antidiabetic Agents

1. **Metformin**: While not specifically approved for MASLD/MASH treatment, metformin provides cardiovascular protection in diabetic patients and may modestly improve hepatic parameters [145, 146].

2. **Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Incretin-Based Combination Therapies**: Incretin-based therapies represent the most rapidly evolving pharmacological class in MASLD management, and internists will increasingly encounter patients on dual- and triple-receptor agonists whose hepatic and cardiovascular effects extend well beyond traditional glycemic indications.
Among selective GLP-1 RAs, liraglutide 1.8 mg daily demonstrated MASH resolution in 39% of patients, compared with 9% with placebo in the LEAN trial, predominantly in patients with type 2 diabetes, and established cardiovascular outcome benefits in the LEADER trial [147, 148]. Semaglutide 2.4 mg weekly achieved MASH resolution without worsening of fibrosis in 59% versus 17% with placebo in the STEP-MASH trial, and subsequently received FDA accelerated approval for MASH in August 2025 based on the ESSENCE trial; cardiovascular outcome data from FLOW and SELECT support its cardiometabolic benefit profile [148, 149]. These agents promote substantial weight loss of 10–15%, improve glycemic control, reduce systemic inflammation, and reduce major adverse cardiovascular events, making them a logical first-choice pharmacological option in MASLD patients with type 2 diabetes or obesity [147–149].
Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist (GIP/GLP-1 RA), achieves superior weight loss of 20–22% and metabolic improvements compared to selective GLP-1 RAs in head-to-head and placebo-controlled trials [147, 149]. The SURMOUNT-NASH trial has demonstrated significant reductions in hepatic steatosis and emerging signals of improved fibrosis with tirzepatide, with full histological outcome data anticipated imminently; cardiovascular outcome data from the SURPASS-CVOT program are maturing [148, 149]. For internists, tirzepatide represents a clinically available option with a compelling cardiometabolic profile. However, MASH-specific regulatory approval remained pending at the time of writing, and prescribing should reflect current approved indications.
Triple receptor agonists – most notably retatrutide, a GIP/GLP-1/glucagon receptor triagonist – represent the next frontier of incretin-based therapy and are entering phase 3 development following striking phase 2 signals. Retatrutide achieved mean weight loss exceeding 24% at 48 weeks in phase 2 trials, with substantial reductions in hepatic fat fraction and favorable cardiometabolic biomarker profiles, including triglyceride lowering and improvements in insulin sensitivity [73, 74]. Phase 2 data for cotadutide, a GLP-1/glucagon dual agonist with direct antifibrotic signaling through hepatic glucagon receptors, demonstrated reductions in hepatic steatosis and liver stiffness in MASLD patients with type 2 diabetes [73, 74]. While phase 3 histological and cardiovascular outcome data for triple agonists are not yet available, internists should be aware of this emerging class, as patients will increasingly inquire about it and early real-world use outside of trials is likely to precede full regulatory evaluation. Appropriate caution is warranted: the magnitude of weight loss does not automatically translate into fibrosis regression or a reduction in cardiovascular events, and long-term safety data for the glucagon receptor agonist component – including effects on bone density, heart rate, and blood pressure – require further characterization in dedicated outcome trials [73, 74].
Across all incretin-based therapies, women, older adults, and patients with lean MASLD were underrepresented in pivotal trials, limiting the generalizability of efficacy and safety conclusions to these populations. Sex-stratified and ethnicity-stratified outcome data from ongoing trials will be important to inform individualized prescribing decisions.
3. **Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)**: SGLT2 inhibitors improve hepatic steatosis, reduce cardiovascular events, and demonstrate favorable effects on heart failure outcomes [150, 151].
4. **Pioglitazone**: Thiazolidinediones improve insulin sensitivity and demonstrate histological benefits in MASH, including steatohepatitis resolution and potential fibrosis improvement, though weight gain, fluid retention, and bone density concerns limit use [152, 153].
5. **Vitamin E (α-tocopherol)**: Vitamin E 800 IU daily is recommended by multiple society guidelines for biopsy-proven MASH in non-diabetic patients without cirrhosis. The PIVENS trial demonstrated MASH resolution in 36% of patients, compared with 21% with placebo, though fibrosis improvement was not significant. Use in diabetic patients remains controversial, given possible increased cardiovascular and prostate cancer risks, and routine supplementation is not recommended without biopsy confirmation of MASH [152, 153].

7.2.2. Lipid-Lowering Therapy

Statins are safe in patients with MASLD and should be prescribed according to cardiovascular risk-stratification guidelines [154, 155]. Statins reduce cardiovascular events without worsening liver disease and may provide modest hepatoprotective effects. Combination therapy with ezetimibe or PCSK9 inhibitors can be used for patients who do not achieve lipid targets [156, 157].

7.2.3. Antihypertensive Therapy

Blood pressure control follows standard guidelines. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are used for their established cardiovascular and renal indications. Observational data suggest possible hepatoprotective effects, though these agents are not recommended specifically for antifibrotic benefit in MASLD, given the lack of robust randomized controlled trial evidence [158, 159].

7.3. Emerging MASLD-Specific Pharmacotherapies

The therapeutic landscape for MASH-specific pharmacotherapy has evolved rapidly. Resmetirom (Rezdiffra), a thyroid hormone receptor-beta agonist, received FDA accelerated approval in March 2024 for the treatment of MASH with moderate-to-advanced fibrosis (F2 – F3), based on the MAESTRO-NASH trial demonstrating MASH resolution in 26% versus 10% with placebo and $\geq$ 1-stage fibrosis improvement in 24% versus 14%; confirmatory cardiovascular outcome data are pending [160, 161]. Subsequently, in August 2025, semaglutide 2.4 mg weekly (Wegovy) received FDA accelerated approval for MASH, based on the ESSENCE trial demonstrating histological benefit in patients with obesity-related MASH [149]. Regulatory status for both agents varies by jurisdiction – neither had received full European Medicines Agency (EMA) approval for a MASH-specific indication at the time of writing – and clinicians should consult current national regulatory guidance, as approvals in this area are actively evolving [73, 74]. Several additional agents remain in late-stage clinical development:

1. **Obeticholic acid**: Farnesoid X receptor agonist showing antifibrotic effects in phase 3 trials, though cardiovascular safety concerns and regulatory decisions require ongoing clarification [162, 163].

2. **Combination therapies**: Trials evaluating agents targeting multiple pathophysiological pathways simultaneously show promise and may represent the next frontier in MASH treatment [164, 165].

7.4. Multidisciplinary Care Coordination

Optimal MASLD management necessitates multidisciplinary collaboration involving internists, hepatologists, endocrinologists, cardiologists, dietitians, and behavioral health specialists [147, 166]. Internists serve critical roles in:

1. Initial identification and diagnosis of MASLD
2. Comprehensive cardiovascular risk assessment and management
3. Optimization of cardiometabolic risk factors
4. Facilitation of lifestyle modifications through counseling and referrals
5. Appropriate specialty referrals for advanced disease
6. Long-term disease monitoring and prevention of complications

The integrated stepwise management algorithm for MASLD in internal medicine practice is illustrated in **(Figure 1)**.

8. Special Populations and Considerations

8.1. Type 2 Diabetes Mellitus

Patients with concurrent MASLD and type 2 diabetes represent a particularly high-risk population requiring intensive management [167, 168]. These individuals demonstrate accelerated fibrosis progression, higher cardiovascular event rates, and increased mortality compared to MASLD patients without diabetes [169, 170]. Prioritization of GLP-1 receptor agonists and SGLT2 inhibitors offers dual benefits for glycemic control, cardiovascular protection, and hepatic improvement [171, 172].

8.2. Lean MASLD

Approximately 7-20% of MASLD cases occur in non-obese individuals (BMI <25 kg/m² in non-Asian populations; <23 kg/m² in Asian populations) [100, 173]. Lean MASLD patients demonstrate distinct metabolic profiles, genetic predispositions, and potentially different cardiovascular risk profiles compared to obese MASLD patients [174, 175]. These individuals warrant equally aggressive cardiovascular risk modification despite normal body weight.

8.3. Elderly Patients

Advanced age represents both a risk factor for MASLD development and a contributor to accelerated fibrosis progression [176, 177]. Elderly MASLD patients face elevated cardiovascular risks and require careful medication selection considering comorbidities, polypharmacy, and altered pharmacokinetics [178, 179].

8.4. Sex Differences, Hormonal Influences, and MASLD

Sex exerts a profound and clinically underappreciated influence on MASLD prevalence, histological severity, fibrosis trajectory, cardiovascular risk profile, and likely treatment response – differences that internists managing cardiometabolic disease must recognize to avoid uniform approaches that may inadequately serve female patients in particular.

8.4.1. Prevalence and Histological Patterns

Premenopausal women consistently have lower MASLD prevalence than age-matched men, with global estimates suggesting a male-to-female ratio of approximately 2:1 in reproductive-age cohorts [6, 20]. This relative protection is largely attributed to the metabolic and vascular effects of endogenous estrogen, which promote favorable adipose tissue distribution, enhance hepatic insulin sensitivity, suppress de novo lipogenesis, and exert anti-inflammatory effects through estrogen receptor-alpha signaling in hepatocytes and Kupffer cells [176, 177]. Despite lower prevalence, premenopausal women who develop MASLD tend to present with less severe steatosis but comparable or greater lobular inflammation than men, suggesting that inflammatory pathways may be activated at lower thresholds of hepatic fat accumulation in this population [176].

8.4.2. Menopause as an Inflection Point

The menopausal transition represents a critical inflection point in female MASLD risk. Estrogen withdrawal at menopause drives visceral adiposity redistribution, worsening insulin resistance, dyslipidemia characterized by rising LDL and triglycerides and falling HDL, and heightened systemic inflammation. This cardiometabolic profile closely mirrors the metabolic underpinnings of MASLD progression [177, 179]. Postmenopausal women demonstrate MASLD prevalence and severity approaching or exceeding that of age-matched men, with accelerated fibrosis progression rates observed in cohort studies following women through the menopausal transition [176, 177]. Early menopause, defined as onset before age 45, has been independently associated with higher MASLD prevalence and more advanced fibrosis, underscoring the dose-dependent hepatoprotective role of cumulative estrogen exposure [177]. Surgical menopause confers particularly elevated risk, with bilateral oophorectomy associated with accelerated steatohepatitis and fibrosis progression in observational data [176, 179].

The cardiovascular implications of this hormonal inflection are equally significant. Postmenopausal women with MASLD face a compounded cardiovascular risk burden: estrogen loss independently accelerates atherosclerosis and increases susceptibility to HFpEF, while MASLD-driven insulin resistance, atherogenic dyslipidemia, and systemic inflammation add further risk layers that may not be fully captured by standard Framingham-based risk calculators calibrated predominantly on male cohorts [131, 132, 177]. Internists should therefore apply heightened cardiovascular vigilance in postmenopausal women with MASLD, and consider whether standard risk algorithms adequately reflect their true cardiovascular burden.

8.4.3. Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), affecting 5 – 15% of reproductive-age women, represents a high-risk intersection of hyperandrogenism, insulin resistance, and MASLD [167, 168]. MASLD prevalence in women with PCOS reaches 35 – 70%, substantially exceeding age- and BMI-matched controls, and fibrosis progression appears accelerated relative to MASLD patients without androgen excess [167]. The shared pathophysiological substrate of insulin resistance and chronic low-grade inflammation renders PCOS-associated MASLD a distinct clinical phenotype requiring integrated endocrine and hepatic surveillance alongside aggressive cardiometabolic risk management [171, 172].

8.4.4. Sex Differences in Fibrosis Progression and Cardiovascular Risk Amplification

While men demonstrate higher overall rates of fibrosis progression across the lifespan, postmenopausal women exhibit fibrosis progression rates that converge with or exceed those of men in

Table 1: Summary of Key Evidence Linking MASLD to Cardiovascular Outcomes

First Author, Year	Study Design	Population (N)	Outcome	Key Findings (Effect Estimate)	Adjustment Variables
Targher, 2016 [32]	Meta-analysis	34 studies N=164,494	CAD/Fatal CAD	OR 1.64 (95% CI 1.26-2.13) for prevalent CAD, HR 1.37 (1.10-1.72) for incident CAD	Age, sex, BMI, diabetes, hypertension, smoking, lipids (varied by study)
Wu, 2016 [76]	Meta-analysis	16 studies N=36,043	Myocardial Infarction	RR 1.64 (95% CI 1.30-2.08) for incident MI	Age, sex, BMI, diabetes, hypertension, smoking, dyslipidemia, and metabolic syndrome components
Targher, 2006 [57]	Meta-analysis	13 studies N=25,837	CV Mortality	OR 2.58 (95% CI 1.78-3.75) for CV death	Age, sex, diabetes, BMI, smoking, hypertension, lipids (varied by study)
Kim, 2018 [26]	Cohort study	N=4,731,801 Korean adults	CV Mortality	HR 1.04 (95% CI 1.00-1.08) for NAFLD vs no NAFLD after 10-year follow-up	Age, sex, smoking, alcohol, exercise, income, BMI, diabetes, hypertension, dyslipidemia, CKD
Mantovani, 2022 [86]	Meta-analysis	11 studies N=2,947,025	Heart Failure (any)	HR 1.50 (95% CI 1.33-1.70) for incident HF	Age, sex, BMI, diabetes, hypertension, smoking, dyslipidemia, CKD (varied by study)
Wijarnpreecha, 2017 [95]	Meta-analysis	5 studies N=320,906	HFpEF	OR 2.10 (95% CI 1.54-2.87) for HFpEF	Age, sex, BMI, diabetes, hypertension, CAD, smoking
Mantovani, 2018 [169]	Meta-analysis	7 studies N=183,419	Atrial Fibrillation	RR 1.23 (95% CI 1.10-1.38) for incident AF	Age, sex, BMI, diabetes, hypertension, smoking, alcohol, heart disease, CKD (varied by study)
Patel, 2016 [28]	Cross-sectional	N=290 patients	Carotid Plaque	OR 2.31 (95% CI 1.05-5.08) for carotid plaque in NASH vs simple steatosis	Age, sex, BMI, diabetes, hypertension, dyslipidemia, smoking
Simon, 2021 [68]	Cohort study	N=2,630 NAFLD patients	MACE	HR 1.69 (95% CI 1.04-2.75) for advanced fibrosis (F3-F4) vs F0-F2	Age, sex, race, BMI, diabetes, hypertension, dyslipidemia, smoking, prior CVD, statin use
Ekstedt, 2015 [66]	Cohort study	N=229 NAFLD patients 26-year follow-up	CV Mortality	HR 3.2 (95% CI 1.5-6.8) for NASH vs simple steatosis	Age, sex, BMI, diabetes, smoking
Mahfood Haddad, 2017 [99]	Meta-analysis	9 studies N=7,944,721	Stroke	OR 1.31 (95% CI 1.14-1.50) for ischemic stroke	Age, sex, smoking, BMI, diabetes, hypertension, dyslipidemia (varied by study)

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; CAD, coronary artery disease; MI, myocardial infarction; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; AF, atrial fibrillation; CAC, coronary artery calcium; MACE, major adverse cardiovascular events; OR, odds ratio; HR, hazard ratio; RR, relative risk; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.

Notes: Most studies were conducted during the NAFLD nomenclature era and are interpreted within the MASLD framework, given 99% diagnostic overlap. Substantial heterogeneity exists across studies in NAFLD/MASLD definition (imaging modality, biopsy criteria), follow-up duration, populations studied, and adjustment for confounders. Residual confounding by shared cardiometabolic risk factors (obesity, diabetes, hypertension, dyslipidemia) cannot be excluded despite multivariable adjustment. Effect estimates should be interpreted with consideration of these limitations.

certain cohorts, particularly in the presence of type 2 diabetes [169, 170, 177]. Advanced fibrosis in women carries cardiovascular risk amplification comparable to that observed in men, with hepatic fibrosis stage serving as an equally potent predictor of cardiovascular mortality irrespective of sex [66, 67]. However, the absolute cardiovascular event rates and the specific manifestations may differ: women with MASLD and advanced fibrosis demonstrate disproportionately elevated HFpEF risk and atrial fibrillation incidence relative to men, consistent with the broader sex-specific patterns of cardiovascular disease expression [83, 84, 91, 92]. A summary of the key evidence linking MASLD to cardiovascular outcomes is presented in **(Table 1)**.

8.4.5. Treatment Considerations

Sex-based differences in pharmacological response to MASLD therapies remain incompletely characterized but are clinically relevant. GLP-1 receptor agonists and SGLT2 inhibitors demonstrate broadly consistent hepatic and cardiovascular benefits across sexes in available trial data, though women were underrepresented in several landmark MASH trials, limiting sex-stratified conclusions [147, 149–151]. Pioglitazone carries particular caution in postmenopausal women given associations with accelerated bone density loss and increased fracture risk, warranting bone health assessment before initiation [152, 153]. Vitamin E supplementation in non-diabetic women with biopsy-proven MASH remains a guideline-supported option, though long-term safety data specific to postmenopausal women are limited [152, 153]. The potential role of menopausal hormone therapy (MHT) in modifying MASLD trajectory and cardiovascular risk in postmenopausal women is an area of active investigation; current evidence is insufficient to recommend MHT specifically for MASLD management, and decisions should be individualized based on established indications, contraindications, and cardiovascular risk profile [177, 179].

For internists, the key clinical takeaway is that sex and menopausal status should be integrated into MASLD risk stratification and management planning. Premenopausal women with MASLD warrant surveillance for accelerated risk transition at menopause; postmenopausal women require proactive cardiovascular risk reassessment; and women with PCOS should be systematically screened for MASLD regardless of BMI. A sex-informed approach to the liver-heart axis is not optional refinement – it is essential to delivering equitable, precision cardiometabolic care.

9. Limitations and Future Directions

Several limitations merit acknowledgment. First, the majority of outcome data cited in this review derive from studies conducted under NAFLD/NASH terminology. However, the 99% diagnostic overlap supports continuity of evidence; prospective validation of cardiovascular outcomes specifically under MASLD criteria remains limited. Second, substantial residual confounding by shared cardiometabolic risk factors – including obesity, type 2 diabetes, hypertension, and dyslipidemia – persists across observational studies linking MASLD to cardiovascular disease, and causality cannot be firmly established from available data. Third, diagnostic heterogeneity is considerable; studies vary widely in how hepatic steatosis was ascertained (ultrasound, MRI-PDFF, histology, or liver enzymes), how fibrosis was staged, and which cardiovascular endpoints were captured, limiting direct comparability across cohorts. Fourth, prospective data generated specifically within the MASLD nomenclature framework are scarce, and the anticipated benefits of the new terminology – including improved disease recognition, reduced stigma, and enhanced patient engagement – have not yet been validated in longitudinal studies.

Despite substantial progress in understanding the MASLD-cardiovascular axis, important knowledge gaps persist. These include elucidating the precise molecular mechanisms linking hepatic fibrosis to cardiovascular outcomes, developing integrated risk prediction models incorporating fibrosis stage alongside traditional cardiovascular risk factors, identifying therapies that simultaneously address hepatic and cardiovascular disease, characterizing ethnic and racial disparities in MASLD prevalence and treatment response, and conducting long-term studies assessing the real-world impact of nomenclature change on diagnosis rates and patient outcomes. Cost-effectiveness analyses of screening strategies and emerging pharmacotherapies also remain an important area for future investigation [180, 181].

10. Conclusion

The redefinition of fatty liver disease as MASLD represents more than nomenclature revision; it embodies a conceptual transformation recognizing the disease as a systemic metabolic disorder with significant cardiovascular implications. The liver-heart axis in MASLD is characterized by complex bidirectional interactions mediated by insulin resistance, chronic inflammation, oxidative stress, atherogenic dyslipidemia, and dysregulation of the gut-liver-heart axis. MASLD significantly increases risks of coronary artery disease, myocardial infarction, heart failure, particularly HFpEF, atrial fibrillation, stroke, and cardiovascular mortality, with hepatic fibrosis stage serving as a critical risk amplifier.

For internists managing patients across the cardiometabolic spectrum, the new MASLD nomenclature underscores the imperative for integrated care that addresses both hepatic and cardiovascular manifestations. Early identification through appropriate case-finding, accurate fibrosis assessment using non-invasive tools, comprehensive cardiovascular risk evaluation, and implementation of intensive lifestyle modifications form the foundation of management. Judicious use of cardiometabolic medications, including GLP-1 receptor agonists, SGLT2 inhibitors, statins, and antihypertensives, provides synergistic benefits for hepatic and cardiovascular health.

The transition to MASLD nomenclature is intended to facilitate better disease recognition, and may reduce stigmatization while aligning diagnostic criteria with pathophysiological understanding and therapeutic targets. As the field advances with emerging MASLD-specific pharmacotherapies and refined risk stratification tools, multidisciplinary collaboration will remain essential to optimize patient outcomes. Internists must embrace their central role in the comprehensive, integrated management of MASLD and its cardiovascular complications, recognizing that successful care requires addressing the liver-heart axis as an interconnected system rather than isolated organ dysfunction. Prospective validation of these anticipated benefits remains an important priority for future research.

Conflicts of Interest

All authors declare no conflicts of interest.

Funding Source

This work received no specific funding.

Acknowledgments

None.

Institutional Review Board (IRB)

None.

Large Language Model

The authors declare that generative artificial intelligence (AI) tools, specifically Claude AI (Anthropic), were used solely to assist in grammar correction and paraphrasing during the preparation of this manuscript. No AI tool was used to generate ideas, analysis, or conclusions. All content was reviewed, verified, and approved by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

Authors' Contributions

HAA contributed to the conceptualization of the study, literature search, data analysis, manuscript writing, and preparation of the original draft, while SAO contributed to manuscript review, critical revision, and editing.

Data Availability

No new data were generated or analyzed in this study. All supporting information is derived from previously published studies cited in the article.

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